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Review

Support Tools in Formulation Development for Poorly Soluble Drugs

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ABSTRACT

The need for solubility enhancement through formulation is a well-known but still problematic issue because of the numbers of poorly water-soluble drugs in development. There are several possible routes that can be taken to increase the bioavailability of drugs intended for immediate-release oral formulation. The best formulation strategy for any given drug will depend on numerous factors, including required dose, shelf life, manufacturability, and the properties of the active pharmaceutical ingredient (API). Choosing an optimal formulation and manufacturing route for a new API is therefore not a straightforward process. Currently, there are several approaches that are used in the pharmaceutical industry to select the best formulation strategy. These differ in complexity and efficiency, but most try to predict which route will best suit the API based on selected molecular parameters such as molecular weight, lipophilicity (logP), and solubility. These methods range from using no tools, trial and error methods through a variety of complex tools from small *in vitro* or *in vivo* experiments or high throughput screening, guidance maps, and decision trees to the most complex methods based on computational modelling tools. This review aims to list available support tools and explain how they are used.

Introduction

Oral drug delivery, specifically solid oral dosage forms, for example, tablets and capsules, is the preferred administration route for the majority of medicines. Such formulations are generally stable, easy to produce, and have accurate doses, in addition to being simple to administer and having generally good compliance. Therefore, most drugs on the market and in development are solid formulations for oral administration. For these to give reproducible and effective *in vivo* plasma concentrations, the drugs need to be readily released and absorbed. However, many new chemical entities (NCE) have a narrow absorption window, being absorbed almost exclusively in the upper part of the small intestine. It is therefore of great importance that such drugs are released completely in the gastrointestinal tract before absorption to avoid low bioavailability.[1] Unfortunately, according to a recent study by Di et al.,[2,3] up to 75% of new candidates in drug development have low solubility. At the same time, around 40% of marketed drugs are poorly soluble.[4] It is therefore clear that poor solubility continues to be a major obstacle in the development of new medicines.[5]

There are a number of methods that can be used to improve the solubility of a drug through the formulation route. Formulation strategies or enabling formulations include particle size reduction, lipid-based vehicles, use of cyclodextrin complexation, formation of salts, polymorphs, and cocrystals, and solid dispersions (as reviewed by Williams et al.[6] and Singh et al.[7]). Identifying which approach gives sufficient solubility and satisfactory chemical and physical stability can take substantial resources and time, especially if many approaches have to be tested to find a suitable one. Furthermore, for those NCEs that are not compatible or soluble in the most commonly used excipients, there is a large number of extra tests that need to be performed to find suitable excipients, ratios of excipients, and processing conditions. Thus, formulation development can potentially be labor intensive and cost and time consuming in addition to requiring a large amount of active pharmaceutical ingredient (API). This latter point is an important issue as, especially in the early development phase, there is sometimes a limited amount of compound available, which can restrict the number and type of formulation approaches that it is possible to test. Without a suitable formulation, an NCE will not be able to progress in the development process.[8,9] Poorly water-soluble drugs intended for oral delivery hence carry considerable risk which can cause higher cost, difficulties in preclinical and clinical trials due to reduced and inconsistent exposure, and therefore increase time to market. There is thus a need for improved efficiency, precision, and prediction in drug development.

As poor solubility is often known early in the development of an NCE, it is important to be able quickly to identify which formulation strategies are available in each specific case. Instead of dealing with

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solubility issues on a project basis, relying to some degree on trial and error, a support tool would be very valuable for giving indications of possible solutions early without having to conduct many experiments. As noted, quantities of NCEs are usually limited early in development and such a tool could greatly optimize the use of what is available. There are some tools currently available that can be beneficial in the earlier or later stages of drug development.[10,11]

The optimal formulation for each specific drug depends on numerous factors, including the required dose, administration route, shelf life, manufacturability, and the physicochemical properties of the drug. Choosing the optimal formulation for a drug is therefore not a straightforward process, and a poor choice of formulation can have devastating effects on the development process for a drug, such as leading to poor clinical data, which in turn can necessitate drug reformulation and prolonged clinical trials, or even termination of the project.[12] Currently, there are several ways that can be used to select the best formulation route for a new drug candidate. These differ in complexity and efficiency and range from trial and error formulations, small scale *in vitro* or *in vivo* experiments, guidance maps, and decision trees to complex computational modelling tools. Figure 1 shows how and where in the formulation development process such support tools can be used.[13] This review aims to shine some light on the available support tools in formulation development and how they can be used.

High Throughput Screening

In any formulation development process, there is a set of most commonly used excipients which are first tested with an NCE. If those are unsuitable, there is a long list of additional excipients, ratios, and processing conditions that can be tested. If no suitable formulation with adequate solubility is found, the drug candidate cannot advance in the development cycle. In such cases, high throughput screening (HTS) is extremely valuable, where it is possible to test a large number of combinations of excipients or formulations using only a very small quantity of API. Furthermore, it is less labor and time intensive than performing the same experiments on a larger scale.[8,9]

For example, Tandem Nano (www.tandemnano.com) has developed a novel HTS method for aiding the formulation development process for nanoparticle formulations. The first part of this emulsion-template freeze-drying screen-based process is building a library of freeze-dried formulations, using combinations of accepted excipients. The second stage includes characterization of the formulations, such as particle size and the capability of redispersion, revealing which excipient combinations work best for the selected API. Using this screening method as many as 1000 freeze-dried particle formulations can be made using as little as 1 mg of API each, thus allowing a rapid selection of a viable formulation without wasting much material.[14] In a recent study, McDonald et al.[15] used this novel HTS for the first time to make a nanoparticle formulation with efavirenz, a non-nucleoside reverse transcriptase inhibitor. Water-soluble polymers and surfactants, 7 of each, were chosen for the study, making 49 formulations. These were freeze dried and characterized to determine which polymer and surfactant best stabilized the efavirenz nanoparticles. Only one polymer, polyvinyl alcohol, was capable of making nanoparticles that completely redispersed to solid drug nanoparticles. The study showed that the screening method was able successfully to optimize the nanoparticle formulation for efavirenz. This emulsion-template freeze-drying platform potentially has broad application for formulation optimization of poorly soluble or poorly bioavailable APIs.[15]

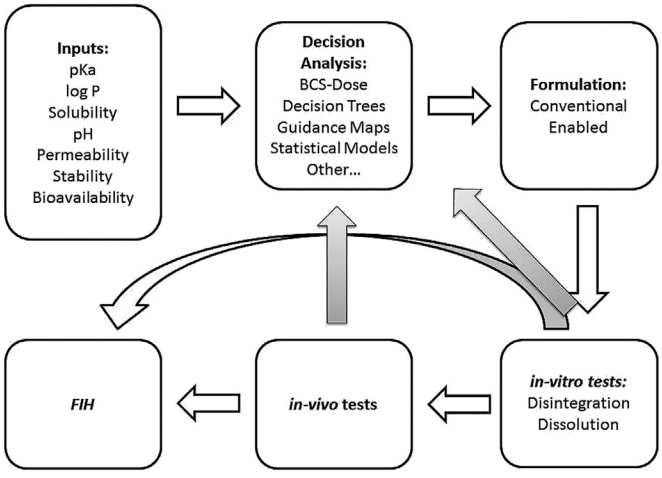

Figure 1. A schematic summary of the formulation decision process in many pharmaceutical companies. The decision analysis step is where the process can be expedited with the use of relevant support tool. Depending on the outcomes of *in vitro* and *in vivo* experiments carried out, the formulation development can go back to the decision analysis step. This process can be repeated until a suitable formulation is found. FIH, first-in-human or the first time the formulation is tested in humans. Adapted from Pearce.[13]

A microscreening method developed by ALZA Corporation, now owned by Johnson & Johnson, rapidly produces and tests hundreds of formulations on a small scale, using only tens of micrograms of API. In this method, drug and excipients are dissolved in an appropriate solvent, such as n-propanol or acetone, and the solution is dispensed into the wells of a 96-well plate. The solvent is then removed using a vacuum centrifuge evaporator leaving the formulation remaining at the bottom of each well, containing 10-40 μg of drug and around 0.4 mg of excipients. The solubility of each formulation can then be tested by adding an aqueous medium into the wells, incubating at 37°C and measuring the drug concentration in solution using high-performance liquid chromatography or ultraviolet spectroscopy.[9]

A screening method for nanoprecipitate formulations, similar to the one described previously, was developed by McDonald et al.[16] The drug triclosan and a polymer, each in varying concentrations with and without the addition of a surfactant (1 of 3), was mixed in a 96-well plate with an automatic liquid-handling robot. The solution was analyzed using dynamic light scattering to check for nanoprecipitation. The samples were then freeze-dried. After redispersion in water, the formulations were reexamined with dynamic light scattering for precipitation. In addition, the formulations were subjected to zeta-potential analysis, and drug concentration in solution was measured by ultraviolet spectroscopy. Size distribution and morphology were examined using scanning electron microscopy. In this study, 252 formulations containing triclosan were produced and tested, many of which showed improved functional properties, in some cases more than 10-fold increase in antimicrobial activity when IC_{50} was tested in *Escherichia coli* and compared to triclosan in aqueous solution.[16]

Dai et al.[8] used the microscreening method to identify a suitable solid dispersion formulation for a compound, using <10 mg. Each formulation consisted of the compound, a polymer, and a precipitation inhibitor. Nine enteric polymers and 7 precipitation inhibitors and their combinations were studied. Each formulation was produced with an evaporation method, and the film produced was then dissolved in simulated intestinal fluid to determine solubility.[8]

The HTS methods described previously can be divided into 2 groups as provided in Table 1. The solvent casting method requires less material as the samples are dispensed as a liquid into a 96-well plate. However, the limitation is that both the API and potential excipients intended for screening have to be soluble in the same